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Of Cats and Rats:

Studies of the Neural Basis of Aggression

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FOREWORD

One of the biggest problems facing contemporary society is human being's aggression toward others and their property: Crime rates for robberies, assaults, and other offenses have been rising steadily for the past few decades. Environmentalists, social workers, and criminologists have been investigating possible social causes behind this problem. At the same time psychologists and neurophysiologists have been studying physiological correlates of aggressive behavior. Through this monograph, the NIMH would like to share with the public the results of a research project on the neural basis of aggression.

What part of the brain controls aggressive behavior? If more than one part is involved, how do they functionally interrelate? What happens in the brain when we are frightened or angry? This report describes research that delves into the brain of cats in an effort to understand the brain mechanisms underlying aggression. The researcher has discovered that various forms of aggression seem to emerge from different stimuli, needs, and brain patterns. The research also indicates that more than one brain component is involved in attack, that there exists in the brain a web of neural pathways that mediate aggressive behavior, and that certain reflexlike mechanisms in the brain are "preprogramed" to respond in certain ways when specific sensory receptors are activated.

As Dr. Flynn says, "I believe the neural mechanisms underlying aggression, defense, and predation can be unraveled." This research should increase our understanding of aggressive behavior and our knowledge of the ways in which an organism is likely to behave when highly aroused. While we must be cautious in extrapolating basic animal research findings to human beings, it is clear that basic research as described in this monograph is both necessary and useful in dealing with human and social problems.

Bertram S. Brown, M.D.
Director
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Of Cats and Rats: Studies of the Neural Basis of Aggression

In a dark alley, with only a street lamp illuminating two seemingly phosphorescent yellow-green eyes, a sudden movement and rustle in the leaves near a trashcan begin the pas de deux of an ancient and swift ballet. Quickly, almost noiselessly, the cat is upon the rat.

Many of us have witnessed such commonplace dramas. Dr. John P. Flynn, together with his scientific colleagues, has been watching them for over 15 years. Instead of the outdoor amphitheatre of the wild, however, the stage has been his well-equipped laboratory at Yale. The purpose of his pursuit: to understand the brain mechanisms underlying aggression. Forms of aggression such as territorial aggression, dominance aggression, sexual aggression, parental disciplinary aggression, predatory aggression, and antipredatory aggression seem to emerge from different stimuli, needs, and brain patterns. And, of course, the forms are frequently radically different. A cat disciplining its refractory kittens exhibits little of the behavior of a cat attacking a rat. Flynn has been focusing on one aspect of aggression—the behavior observed when a cat attacks a rat.

A cat, like many other mammals, including man, has capacity for being mean and vicious in a variety of ways, depending on the circumstances and the cat's own temperament. The cat's varied repertoire is familiar: the icy, silent stalking and killing of prey; the spiky-backed wild yowling, spitting, and clawing when on the defensive; the somewhat similar but less emotional confrontation of two competing males. The basic question for a physiological psychologist such as Flynn is: What parts of the brain control aggression and how are they functionally interrelated?

To answer such a question, a scientist has to wear intellectual bifocals. He has to look both at what the cat is doing, and what its brain is doing. Prior to the late 1920's, scientists couldn't study both aspects simultaneously during aggression. They could observe and manipulate the brain surgically while an animal was anesthetized, and later study its behavior to discover the behavioral effects of their interventions and deduce from their observations the functional role of severed or removed (ablated) brain areas. However, studying brain activity in the awake and active intact animal was technologically impossible. Early in this century, several key ablation studies had suggested that one type of aggression, the "rage" behavior seen when a cat is on the defensive, seemed to be under the control of the hypothalamus, an area located at the floor close to the midline of the brain, below the cerebral cortex and thalamus, and above the pituitary gland. (Descriptions of brain areas appear in the Glossary.) The hypothalamus, a part of the "old brain," is now known to contain centers controlling a number of body functions, such as regulation of body temperature, eating, and sexual activity, or, as a medical student mnemonically puts it: "fear, feeding, fighting, and fornication." Despite considerable presumptive (although sometimes contradictory) evidence of the role of the hypothalamus in rage behavior, no one had directly demonstrated that when certain areas of the hypothalamus are activated electrically, aggressive behavior results.

Background

In the late 1920's, W. R. Hess, of Zurich, who had been studying the role of the hypothalamus in the "emotional" behavior of cats, developed a technique which has since become a cornerstone of modern physiological research on the brain. He found that fine electrodes could be permanently implanted in the brain and used to stimulate neural activity in a rather specific brain site by conducting an electric current. Later, others extended the technique to record the brain's electrical activity or to destroy selectively small segments of neural tissue. (As a recording device, implanted electrodes provide information similar to that obtained by an EEG, but since they are situated in the brain and not on the scalp, the information is more precise and localized.)

A cat with electrodes implanted in the hypothalamus behaves normally, once it has recovered from the initial implantation operation, if the electrodes are inactive. But when the brain is stimulated, the cat's normal ongoing activity is changed and it does whatever its brain is "told" to do by the brain cells under stimulation. Stimulation through a solitary electrode in a tiny portion of brain tissue can elicit a very complex pattern of behavior.

As Hess discovered in using this technique, a previously placid cat, when stimulated in the hypothalamus, can turn into a raging terror: fur erect, ears back, pupils dilated, tail lashing, spitting, hissing and growling, claws out and slashing at almost anyone or anything (including, of course, an unwary experimenter). When the stimulation ends, the cat usually stops cold, as if frozen or puzzled, and then resumes its placid routine as if nothing extraordinary had happened. Given the artificiality of the situation, some scientists then, as now, have asked: Does the "rage" elicited by hypothalamic stimulation actually reflect the cat's emotional state, or is it more a function of merely activating a certain motor apparatus, without eliciting the actual emotion of anger?

As so often occurs in science, while Hess was conducting his studies of cat emotionality, Philip Bard of the United States, using the technique of surgical removal, localized the "sham" rage mechanism in the posterior of the hypothalamus. Bard's discovery led him to suggest what has been called a hypothalamic theory of emotion, which, in turn, stimulated an eruption of research to elaborate the mechanisms of emotion—especially of rage. Flynn is the intellectual descendant of Hess and Bard in carrying on the search for the brain mechanisms of attack. The debate over whether this type of behavior is real or "sham" rage has now somewhat subsided, as many scientists such as Flynn have chosen to study the relation between elicited brain activity and behavior, without speculating on the emotions of animals.

Over the next few decades, following Hess' technological breakthrough and the demonstration of hypothalamically induced rage, a number of ablation studies, as well as a brilliant speculative paper by James Papez, suggested that aggression in cats is not controlled by the hypothalamus alone. Many nearby or functionally interconnected areas in the brain also seem to be involved.

By the time Flynn entered the field of aggression research in the early 1960's, it seemed likely that there was no single brain center for aggressive behavior. Instead, there was a dynamic interplay of checks and balances exerted by several interconnected brain areas acting upon one another, some of which turn other areas on or enhance their activity, while others turn them off or diminish their activity.

There have been other changes in the field as well. As humans in the 1950's and 1960's became increasingly concerned with their own aggressive tendencies, there was a burst of scientific interest in studying spontaneous aggression among humans and other animals—aggression toward members of their own species and other species. As a result, a rapidly growing body of evidence—from both the laboratory and naturalistic settings—suggested that the nature of aggressive behavior depends in part on the animal's social situation and the way the animal perceives it. (Think again of the difference in a cat's aggressive behavior when confronted with a mouse, a dog, or another competing cat.)

A Classical Experiment

Flynn began his studies of aggression in cats with social-environmental conditions in mind. He and Marvin Wasman, a coworker, decided to use Hess' technique to elicit attack behavior in cats, but they added a crucial new element into the experimental paradigm: a rat. Hess had claimed that in hypothalamically induced rage, a cat strikes out in an undirected and undifferentiated way. Others claimed that this undirected display was a "sham" rage—unconnected with an emotional state. Wasman and Flynn decided to place a rat in the cage to determine whether the cat would direct its fury at a target.

They deliberately chose as their subjects cats that did not normally attack rats. (Nursery rhymes notwithstanding, most cats, at least in the laboratory, regard rats with indifference.) They reasoned that the demonstration of an unlikely event—a rat attacked by a normally indifferent cat—would provide more convincing evidence of neural stimulation effects than would the elicitation of a behavior pattern that was naturally highly likely.

The experimenters, stimulating the cats in the same hypothalamic areas as had Hess, expected their subjects to attack rats in a rage, furious bundles of affect. Nine of the fifteen subjects did. But Wasman and Flynn got more than they bargained for. In addition to demonstrating for the first time that hypothalamic stimulation could elicit a directed rage attack on a rat, the experimenters discovered that a second type of attack behavior could also be elicited from the hypothalamus—what they termed "quiet attack." Five of the cats which attacked the rat showed only this style of attack. Instead of attacking in a wild rage, they were cool and stealthy. With very little wasted movement and few vocalizations, and only a ridge of hair standing on end, in short, no irrelevant behavior interfering with their efficiency as killers, these cats did not slash with their claws. They merely held down their prey and dispatched them neatly, frequently with one bite on the back of the neck. This, then, was the chill professionalism of predatory attack.

Not all of the cats tested showed a pure type of attack. Four cats were "switch hitters," using either quiet or affective (rage) attack, depending on the precise part of the hypothalamus being stimulated. One independent cat, which showed evidence of rage, nonetheless did not attack the rat.

Because the hypothalamus also plays an active role in controlling eating, Wasman and Flynn were concerned that attack behavior might have simply been elicited because hypothalamic areas controlling biting and eating were activated. To test this possibility, the cats were restimulated while food, instead of rats, was placed in their cages. Some cats prowled, came up to the food dish, savagely bit the food and continued to prowl, but never swallowed the food. Others, although clearly aroused, ignored the food dish. The experimenters concluded that they were not stimulating eating behavior.

Wasman and Flynn, interested also in the kinds of natural stimuli toward which cats directed their attack, briefly explored the responses of these same hypothalamically stimulated cats to inanimate objects. While all of the cats showed some aggressive responses to a dead rat, their attacks were unsustained. When given the choice of a dead or live rat, they clearly preferred the live one. They would deliver a passing swipe or bite to a stuffed toy dog or rat, but would then move on. (Flynn and his coworkers subsequently conducted more systematic investigations of the sensory side of aggression, which will be discussed later.)

Following repeated behavioral trials with the same cats, Wasman and Flynn studied the cats' brains anatomically to confirm the sites of stimulation and to correlate behavioral observations with brain structures. They found that attack behavior had been elicited from many points in one section of the hypothalamus: its lateral (or side) portion. The pure affective or rage attack had been evoked by stimulating points very close to but somewhat nearer the midline than the sites responsible for pure quiet stalking attack. The cat which had been aroused but did not attack had had electrodes in slightly higher locations than the others.

As Flynn was to realize later, quiet attack probably would not have been discovered in the absence of a mouse or rat. Although, as Wasman and Flynn demonstrated, affective attack can be directed toward a rat, it can also occur, as it did for Hess, with no animal target available. Quiet attack, by contrast, will occur only when an appropriate target is present.

Flynn's Line of Inquiry

Over the decade and a half since the Wasman-Flynn studies, Flynn and his associates have explored in great detail the brain mechanisms involved in attack when a rat is present. As their studies have progressed, their findings have suggested a rather surprising new view of the total organism's readiness to fight. In summary, their own work and that of others have shown that:

1. There are several types of attack behavior that can be elicited by brain stimulation: quiet attack, affective attack, and various mixtures of the two (including "affective display" in which cats scream or snarl, with hair raised and pupils wide open, with no attack). The type of attack elicited depends on the precise locations where stimulation occurs and on the strength of the stimulation.
2. There is no single geographical area or "center" in the brain which is solely responsible for attack behavior. Rather, there is a network of physically and functionally interconnected brain parts which have separate but somewhat overlapping functions in producing various types and components of attack behavior. Some brain organs which appear to be anatomically distinct and unitary nonetheless are functionally subdivided, with their subsections having different, and sometimes contradictory, roles in attack.
3. The brain areas involved in attack include the hypothalamus, thalamus, midbrain, stria terminalis, and the amygdala. Some of these sites, such as the hypothalamus and the midbrain, yield both quiet and affective attack in stimulation. Others, such as the amygdala and stria terminalis, yield only affective attack. Only quiet attack can be obtained from the thalamus. Although midbrain stimulation in some areas can give rise to both pure types of attack, in most parts of the midbrain affective display results, but no attack.

Although all these brain areas are within "shouting distance" of each other (mostly less than a centimeter), they have different topographic characteristics—an almond shape here, a sea horse there, and a tweed of gray matter or bundles of neural conduit connecting them. One of the implicit tenets of physiology is a belief that anatomical distinctions are related to functional ones. Thus, even if similar attack behavior could be elicited by stimulating different anatomical sites in the brain, each site must be playing its unique role in the overall mechanism coordinating attack. One important aspect of Flynn's studies has been an attempt to elaborate and explain the role of each contributing member of the cast of the brain mechanisms. This has been driving Flynn toward a search for all the parts of the cat's brain directly concerned with attack and for answers to how the various parts affect one another in ultimately unleashing an attack.

Based upon his studies of the brain areas involved in quiet attack on a rat, Flynn has developed a "model" or description of the way the nervous system is organized for attack. In Flynn's view, the brain areas that give rise to attack behavior on stimulation all are part of an interconnected system which regulates attack. Flynn calls them "patterning mechanisms," because their excitation (through stimulation) imposes a specific pattern of excitation on other parts of the nervous system. The patterning mechanisms are all rather directly connected anatomically to one another and to other parts of the nervous system that bring in sensory messages from the outside and send messages to the motor system to take action. Patterning mechanisms, or attack areas of the brain, are also connected physically and functionally to other brain areas from which attack cannot be directly elicited by stimulation. Presumably, these latter areas play a regulatory role, although they are rather remotely removed from direct influence on the sensory and motor systems.

When quiet attack areas are stimulated, the cat does not simply go into a state of diffuse arousal and "rage"; rather, it behaves in a special way—an organized pattern of reflexes is released, consisting of approaching a rat, striking at it, placing a paw on it, lunging at it, and biting it. But the cat behaves in this way only if a rat (or something very rat-like) is in its environment. Thus, quiet attack is under some sort of sensory control and requires the right sensory as well as central stimulation to elicit it. (Even affective attack, which is less dependent on the characteristics of the environment, is affected somewhat by sensory input.)

Flynn has found that attack behavior can be analyzed experimentally by studying a number of its smaller behavioral units, which he calls "patterned reflexes." Each one of these components of attack behavior involves a discrete "package" of sensory and motor activity. For example, looking at just one component of attack behavior, the patterned reflex of biting a rat, the cat must see and/or feel the rat to bite it. It does not simply bite indifferently when its hypothalamus is stimulated. But if it gets the right sensory stimulation, it will almost invariably bite when stimulated in an attack site. It is as if cats store a number of computer programs that are called into operation at the appropriate time, depending on the context. But aside from the obvious differences, a cat's brain is not like a computer. It is more like a military command center that is continually dealing with routine messages. In such a center, at critical times, a message comes in and, after some brief delay for marshaling the proper resources, causes a fast buildup in activity, followed by a fairly gradual letdown after coping with the emergency. In physiological terms, there is some level of neural activity at all times, followed by a short delay between the time of stimulation and the resulting change in neural activity and behavior. Then, after the stimulation stops, there is decay of activity in the brain until the routine levels are reached again. Following the short letdown, the cat is ready to repeat the process.

Since quiet attack depends on the right sensory stimulus (a rat or rat-like object) being present, this suggested to Flynn that when a quiet attack site is stimulated, a pattern of excitement is set up in the nervous system which sets both the sensory and motor systems of the animal into a state of readiness for attack. If the right stimulus is present, a chain of reflexes is set off, each reflex involving a predetermined linkage of sensory and motor activity. If a cat's brain "talked" to itself, an attack area under stimulation might say something like:

> I'm excited! For some reason, I feel ready to take on the world. Eyes, feelers, fur, check what's out there. Limbs, get ready for action. Now, paw, if you find out that there's anything furry or rodent-like out there, get ready to strike. Mouth, you too, get ready to bite when you feel fur.

Once the "right" sensory stimulation occurs, the "right" motor pattern is essentially automatically released. Flynn and his colleagues have demonstrated that unlike normal reflexes, which can be elicited any time the proper sensory stimulation occurs (like an eyeblink to a puff of air), patterned reflexes occur only when both the brain and the sensors are primed.

When an attack area is stimulated, more than patterned reflexes are set off, although they comprise much of what we recognize as attack. Depending on the attack site, there are also various components of affective display: raised hair, dilated pupils, vocalization, etc. There seems to be some overlap between the areas and systems that regulate affective display and those that regulate the two types of overt attack, with affective attack involving more components of affective display and quiet attack less.

Flynn and his coworkers have also studied how the various areas of the brain involved in attack are interrelated. They have concentrated on those brain areas from which attack behavior can be directly elicited (patterning mechanisms), but have included some areas, such as the hippocampus, which lack known attack sites but do, however, have anatomical or functional links to the patterning mechanisms.

For Flynn, the state of readiness to fight, as produced by stimulation in an attack area, is not simply central and diffuse: It already involves sensory and motor elements in the pattern of excitation. Flynn's work has also suggested that the sensory effects of quiet attack area stimulation in the hypothalamus are very precise. If only one side of the hypothalamus is stimulated, one side of the body will be appreciably more receptive to sensory stimulation than the other. This lends further credence to the view that attack behavior does not stem from some diffuse "emotional" or "drive" state.

In the following sections we will examine some of the specific studies conducted by Flynn and his colleagues that have contributed to his view of the neural basis of attack behavior. Two main questions will be discussed:

1. Which patterned reflexes are involved in attack, and how are they set off by sensory stimulation?
2. Where are the patterning mechanisms for attack behavior, and how are they interrelated?

Patterned Reflexes

To use a rather crude and mechanistic analogy, a patterned reflex is like a sophisticated music box: Wind it up, press the right "go" lever, and out comes a preprogramed melody, but only if it senses that the tune is right for the occasion. In an extensive series of studies, Flynn and his coworkers, particularly Malcolm MacDonnell, have examined several of these patterned reflexes, concentrating on the sensory conditions that set them off. The first of these experiments explored the relative importance of various sensory systems in eliciting quiet attack with hypothalamic stimulation. The investigators were asking: When a cat perceives a rat and attacks it, which sensory systems are telling it to attack—vision, touch, smell, or all of these—and which are most important to the cat? They found, through several studies in which attack behavior was examined in the presence of selectively introduced sensory deficits, that contrary to popular opinion, the sense of smell is not critically important in attack behavior. (Humans may cry "I smell a rat!", but cats do not, at least not in Flynn's laboratory.) The visual and tactile systems, however, are essential. Within the tactile system, the muzzle and forepaws are particularly sensitive.

Tactile Patterned Reflexes

Looking at intact animals with no sensory defects, MacDonnell and Flynn found two reflexes of the head and mouth in response to touch that are part of the overall pattern of attack behavior. In an unstimulated cat, touching its muzzle evokes almost no behavioral response except perhaps occasionally a slight closing of the lips. But under hypothalamic stimulation, if the muzzle area between the upper lips and nose is touched lightly, the cat will move its head to bring its lips in contact with the stimulus. When the lips are touched, the mouth snaps open like a spring (presumably ready for biting). When MacDonnell and Flynn severed the trigeminal nerve which brings in sensory information from the muzzle, this reflex did not occur, again underscoring the necessity for incoming sensory information to set off the reflex.

Here, then, is an excellent example of a patterned reflex. When brain stimulation occurs (which presumably sets off a patterning mechanism of neural activity), the proper sensory information from the mouth area sets off the motor control of lips and mouth needed for biting attack.

Two characteristics of these tactile patterned reflexes are of particular importance to Flynn. First, the greater the intensity of hypothalamic stimulation, the larger the area around the muzzle that produces this response. Thus, with greater central excitation, the sensory system becomes more receptive; with a wider area of sensory responsiveness, attack becomes more likely. Second, the size of the muzzle area in which stroking will trigger a response differs on the two sides of the muzzle; it is larger on the side opposite (contralateral to) the site of hypothalamic stimulation. Thus, if only the left side of the hypothalamus is stimulated, there will be a larger receptive field on the right side of the muzzle than on the left. (This "laterality," or control by one side of the brain of the opposing side of the body, reflects the basic "wiring" of the brain to the periphery.) This finding suggested to Flynn that hypothalamic stimulation does bring the reflex into play, but with different degrees of excitation on the two body sides.

Flynn and Richard Bandler have examined another tactile patterned reflex which operates in a similar way. A cat without electrodes compelling its responses usually will not react to a stroking or rubbing of its forelimb, except perhaps occasionally to lift its paw. When a cat is stimulated in a hypothalamic attack site, it will strike at any object that touches its forelimb: light wire hairs, cotton swabs, tongue depressors, or, best of all, an anesthetized mouse. One stroke: one strike. The area of responsiveness on the forelimb, as in the study of mouth area sensitivity, widens with increased stimulation. The striking response is also brisker. As in the previous experiment, there is a wider area of responsiveness on the leg opposite the stimulated side of the hypothalamus. Here again we seem to see an integrated relation between brain processing, sensory input, and motor input, with each element closely coordinated with the others.

Visual Patterned Reflexes

As Bandler and Flynn have also shown, patterned reflexes in the hypothalamically stimulated cat can be set off by what it sees as well as by what it touches. If a mouse is presented to a restrained cat that is only permitted to move its head, the cat, unstimulated, will not lunge at the mouse. But if an attack site in the hypothalamus is stimulated, the cat will rapidly move its head forward and open its mouth at the sight of the mouse; if permitted, the cat will also viciously bite the mouse. To elicit this behavior, the mouse must be quite close to the cat—within 2–2½ inches. If the mouse is shown to only one eye at a time, the cat is more likely to lunge when it views the mouse through the eye opposite the stimulated hypothalamic side.

Stimulation of the hypothalamus affects the cat's visual system, although no clear anatomical paths are yet known between the hypothalamus and the visual system. How then does the hypothalamus "tell" the visual system to watch out for rats? Flynn and Carl Chi decided to find out the nature of such neural communication. They recorded the electrical signals at several known points of the visual system during individual stimulation of the hypothalamus and midbrain. Stimulation at both sites affected the brain's responses at the visual cortex, suggesting that even if the anatomical connections are as yet unknown, there are functional and physiological links between the subcortical attack areas and the higher cortical areas that process visual information. These results support, at the physiological level, the implications of Flynn's behavioral studies of patterned reflexes. The main point, for Flynn, is that the hypothalamus works intimately with the sensory and motor systems, setting up and facilitating specific, discrete patterns of receptiveness to environmental stimulation, each of which is linked to a particular pattern of motor response. In Flynn's view, hypothalamus stimulation does not set off a general internal state which facilitates attack in general. If this were so, there would be none of the laterality seen in the patterned reflex experiments; hypothalamic stimulation would facilitate sensory responsiveness equally on both sides of the body. Thus it appears that it is not "aggression" or a particular "drive" that is being stimulated, but rather a specific neural pattern linking the point of stimulation to a sensor—in this case, the eye.

When quiet attack points of the hypothalamus are stimulated, the cat becomes a killer, but a choosy one. It is not simply told by its brain to attack. It is made ready to attack if certain conditions in the environment are right, such as the presence of an appropriate rodent target. At the behavioral level, one can identify the cat's preferred targets, as P. K. Levison and Flynn have done. Nine cats, under stimulation of quiet attack sites in the hypothalamus, were given the choice of an anesthetized rat, a stuffed rat, and either a hairy toy dog, a foam rubber block, or a polystyrene block. Seven of the nine never bit the foam rubber or polystyrene blocks, but eight of the nine regularly chose either the stuffed or the anesthetized rat.

As yet the neural mechanisms underlying the cat's perceptual selectivity are largely unknown, but there are clues from the previously cited study by Bandler and Flynn that a certain amount of sensory selectivity is built into the small patterned reflexes that make up attack behavior. In the cat, which will strike in response to stroking by a variety of objects, the response is more reliably elicited if the object is soft and furry—especially if it is a rat or mouse. It seems as if the cat is "preprogramed" to respond in certain ways when specific sensory receptors are activated.

The general point for Flynn is that under stimulation, certain very specific neural pathways, on both the sensory and motor sides, are bound together in a discrete package which becomes overt behavior when the environmental conditions are right.

Patterning Mechanisms

The discovery that there are numerous brain areas from which attack can be elicited (such as the hypothalamus, thalamus, midbrain, stria terminalis, and amygdala) suggested to Flynn and others that these are probably functionally interrelated in the regulation of attack behavior. In addition, a growing body of neuroanatomical evidence suggests that they are physically interconnected by nerve cells adjacent to one another.

One approach to discovering how brain areas interact is to stimulate two simultaneously and see whether the normal response from one is augmented (facilitated) or diminished (inhibited) by stimulation in the other. Presumably, during attack, many parts of the brain are simultaneously active and excited, exerting influences back and forth to regulate one another. Thus, simultaneous stimulation provides a miniature model of some of these interactions and suggests the type and direction of control each exerts over the other. Such studies suggest functional interrelations between the brain areas stimulated, but do not, of course, reveal how these interrelations are related to the rest of the brain's activity.

Simultaneous Stimulation of Two Brain Areas

Quiet attack can be elicited by stimulation in certain areas of either the hypothalamus or the midbrain. What happens if both areas are stimulated simultaneously at various levels of intensity? Do they somehow cancel out one another or add up to enhanced attack? If both sites are stimulated at levels normally too low to elicit attack, will the combined signals result in attack? These are the kinds of questions Flynn and Michael Sheard, a coworker, asked as they studied the interaction of midbrain and hypothalamus. The original design of the Wasman-Flynn study was used, but electrodes were placed in both the hypothalamus and midbrain. Attack behavior elicited from each area alone was first observed before the combined effects were studied. Both quiet and affective attack could be obtained from either area, depending on the precise stimulation site and the intensity of stimulation. When both areas were stimulated in effective attack areas, at intensities known to elicit attack, all nine cats tested attacked rats faster and with greater intensity than they had under hypothalamic stimulation alone. Stimulation at many different midbrain points could facilitate hypothalamically induced attack. Subsequently, Sheard and Flynn asked: If you stimulate both areas at intensities insufficient to elicit attack from either one individually, will their combined effect result in attack? And if you combine midbrain stimulation at a level too low to elicit attack with hypothalamic stimulation at an attack-producing level, will the cats attack more rapidly? The answer to both questions was, yes.

In another part of the study, Sheard and Flynn showed additional evidence of the functional linkage between the midbrain and hypothalamus. When attack areas in the hypothalamus were stimulated, there was EEG evidence that electrical activity was evoked in the midbrain. Similarly, attack-area stimulation in the midbrain produced evoked electrical activity in the hypothalamus.

These results, taken together, suggested to Sheard and Flynn that the midbrain acts as an amplifier for effects elicited in the hypothalamus. That is, however the cats reacted when stimulated in the hypothalamus, the effects were enhanced by simultaneous stimulation of the midbrain. But the evidence was not clear cut. Stimulation of some parts of the midbrain in combination with hypothalamic stimulation either produced no facilitation or actually suppressed attack previously elicited from the hypothalamus.

The midbrain clearly affects the hypothalamus in eliciting attack, but does it need the hypothalamus at all? Could the hypothalamus simply be a spare part to be used when the midbrain is not operating properly? What is attack behavior like when the midbrain is intact but the hypothalamus is removed? Flynn and G. D. Ellison investigated this question by comparing the behavior of intact cats with those in which the hypothalamus was surgically isolated (which is tantamount to removal). They found that the cats would attack mice even without the hypothalamus. Thus, they showed that the hypothalamus is completely unnecessary for attack. However, the cats with no hypothalamus were much less spontaneous in their actions than intact cats—almost, one might say, "catatonic." Although cats would attack if strong stimuli were used, such as clamping the cats' tails, they hardly moved between attacks. On the basis of this evidence, Flynn concluded that while the hypothalamus is not necessary for attack, it probably does function in a normal cat, adding spontaneity to the animal's behavior. But because the technique of surgical isolation might reduce activity and spontaneity through the systemic effects of surgical trauma alone, we cannot yet be certain of the relative roles of the hypothalamus and midbrain. (Even losing a leg may cause someone to be quiet for a while. Can we say that therefore the legs are implicated?)

In a following study, Flynn moved from the midbrain to a part of the brain very close to the hypothalamus—the preoptic area. He asked: What happens to attack behavior elicited from one part of the hypothalamus when an area very near to it (which some would consider as part of the hypothalamus) is stimulated simultaneously at known attack sites? This question was answered by Barbara Inselman and Flynn, who found that the attack effects of concurrent stimulation in the hypothalamus and the nearby preoptic area depend on which part of the latter area is stimulated. That is, although the preoptic area seems to be a homogenous piece of brain tissue, its parts clearly have very different roles and brain functions. In general, hypothalamic attack is facilitated by stimulation in the middle or side of the preoptic area and is suppressed by stimulation in the periventricular part of the preoptic area. However, some hypothalamic attack sites resist suppression. In those that do not, the suppression effect is long lasting, suggesting to the investigators that preoptic stimulation may set off a hormonal or biochemical reaction. The data also suggested that during simultaneous stimulation, the attack-eliciting effects of the hypothalamus on the preoptic area are stronger than those of the preoptic area on the hypothalamus. The experimenters concluded that the hypothalamus, although itself regulated by other brain areas, also has a reciprocal effect on some of them.

In addition to studies of the interactions of brain areas known to elicit attack, Flynn and his colleagues have studied how hypothalamically induced attack is affected by simultaneous stimulation in related brain structures that have no attack sites. Allen Seigel and Flynn paired stimulation in the hypothalamus and the hippocampus, long implicated in emotional behavior. If Papez was right, then the hippocampus, together with the hypothalamus and others, is part of the brain subsystem responsible for emotion. The design was similar to the Sheard and Flynn study. Siegel and Flynn found that while stimulation of one part of the hippocampus (the ventral or front part) accelerates attack, stimulation of another part (the dorsal or rear part) slows it down, suggesting that the hippocampus is functionally divided. This impression was supported in part by other evidence showing that when the apparent source of enhanced attack, namely, the ventral hippocampus, is destroyed by lesions, the speed of attack is reduced.

Neurophysiological studies such as most of those cited above are beginning to suggest some of the checks and balances operating in the central control and regulation of aggressive behavior. They represent one of several approaches to the problem, namely, a functional description of interconnections in the brain. Flynn and his coworkers have also used another approach: a structural description of brain interconnections based on neuroanatomical studies. If Flynn could identify the specific brain areas and linking pathways related to attack, he could integrate them with the results of neurophysiological and behavioral studies to begin to build an explanatory model of the attack mechanism. Indeed, the anatomical studies have yielded a wealth of suggestive data implicating parts of the brain in the process and reinforcing the results of other studies.

Neuroanatomical Studies

Chi and Flynn have combined the basic Wasman-Flynn design with classical neuroanatomical techniques to describe some of the pathways leading from the hypothalamic attack sites to other parts of the brain. After identifying these attack sites through electrode stimulation, the electrodes were used to destroy small areas of neural tissues surrounding them. After these lesions were made, the cats were again stimulated, but with much higher currents than were previously needed to obtain attack. When there was no response, it was assumed that the lesion was just large enough to eliminate that portion of the tissue associated with attack elicitation. For each attack site, the cat's behavior was carefully recorded before and after the lesions. Such behavior as "bit a rat on the head and neck," "struck rat with paw," "pupillary dilation," "meowing," "growling," "hissing and spitting," "ate food," and "tried to escape from cage" were part of the behavioral inventory. Once it was clear that the lesions were effective in eliminating attack behavior, the cats were anesthetized and killed; the brain areas that had been close to the electrodes were examined under a microscope. The investigators were able to trace the neural pathways issuing from the hypothalamic attack sites through a well-known technique that capitalizes on the tendency of nerve cells to degenerate when they die. The degeneration spreads along the length of the nerve cells until it reaches the space (synapse) where it meets another cell. Degenerated nerve cells can be marked for easy identification through the use of chemical dyes that attach themselves to and mark degenerated tissue. One then can look at various parts of the brain for evidence of degenerated nerve cells. The degeneration technique enables neuroanatomists to draw a "wiring diagram" of the way hypothalamic attack sites are anatomically connected within the hypothalamus and beyond. While the wiring diagram does not reveal the functional relationships among connected elements of the brain, it can suggest where to look for them and can confirm neurophysiological and behavioral results already recorded.

Chi and Flynn, following this procedure, have found that for cats that had reacted to hypothalamic stimulation with quiet attack, the degenerative pathway led up from the hypothalamus through the preoptic area into the septum; it also descended from the hypothalamus into the midbrain reticular formation and ultimately into the central gray substance of the midbrain. There was also degeneration into the dorsal hypothalamic area and the midline thalamus. The end points to which degeneration was traced correspond well with known areas for eliciting attack behavior. Again, the evidence points to a linkage among the major brain areas which individually are known to be involved in aggressive behavior.

So for Flynn, it isn't simply that the hypothalamus or some other site causes attack. Rather, the brain is like a mosaic, each tile of which may be meaningless, but where the complete aggregation or pattern suggests a scene.

The Natural History of Attack Behavior

In its attempt to cope with the environment, it is clearly an advantage to the cat to have reflexes which, when attack is needed, ready its paws to capture and hold its prey when making contact with it. The same can be said for other patterned reflexes which appear to be in the service of predatory or defensive behavior. This explanation, however, is as yet conjectural; it depends to a large extent on the degree of similarity between electrical stimulation of the brain and natural stimulation in the wild. A crucial question, of course, which has not yet been answered is: What are the natural conditions that activate the hypothalamus? The answer to such a question lies outside the realm of Flynn's inquiry. He obviously starts his investigation at the point when the hypothalamus is already activated—by him.

Flynn is well aware that the attack behavior he observes in the laboratory, and its apparent neural basis, may not be the same as that which occurs naturally. Not only is he forcing the brain to act, through potentially disruptive means, but he is working with a special population of cats, selected because they do not naturally attack rats and are made to behave in ways that are unnatural for them. (We do not, of course, know whether these same experimental animals, which are not naturally ratters, would naturally be mousers.) Possibly there are aspects of their brains' structure or function that are different from those of natural ratters.

There are other artificial aspects to this research. The rats, for humane reasons, are mostly anesthetized and cannot run around. The cats, living and tested in cages, exist in a very restricted environment and undoubtedly have had different life experiences from the average pet cat or alley cat. The list is endless.

When a scientist selects out a portion of the natural world for investigation in the laboratory, he or she takes a calculated risk. In exchange for a loss of naturalness, spontaneity, and "reality," presumably essential aspects of a natural phenomenon can be carefully manipulated and observed more precisely than they can outside the lab. Flynn has gambled that the two main types of attack he so painstakingly studies, which at least superficially resemble closely behavior seen spontaneously in the wild, are in their essential elements the same as attack in the wild. That is, the same basic neural mechanisms are relevant in both situations.

Flynn has advanced the physiological research of aggression appreciably by adding to the laboratory one crucial element from the natural environment of cats: a living prey. He and other researchers in the future will undoubtedly advance the field still further by minimizing the discrepancy between the lab and the wild—both by creating a more natural environment in the lab, and by discovering methods to study the interaction of behavioral and neural patterns in spontaneous aggressive behavior of free cats.

Glossary

Amygdala:	An almond-like part of the subcortex that gathers signals connected with the sense of smell and other visceral information essential to the function of the limbic system.
Hippocampus:	A seahorse-shaped part of the subcortex with two protuberances, situated on the floor of the brain, near one of its three "holes" or ventricles. It is thought to be involved in memory and emotion.
Hypothalamus:	A part of the subcortex located below the thalamus and above the pituitary gland and midbrain reticular formation. It is connected rather directly with the amygdala, hippocampus, midbrain reticular formation, thalamus, and stria terminalis, and is almost anatomically continuous with the preoptic area. Sometimes called "the metronome of the body," it correlates information about the inner state of the organism with sensory information to influence motor and hormonal responses. Its specific functions include correlation of taste, visual and olfactory information; control of the peripheral part of the nervous system; and regulation of appetite, growth in young organisms, water and chemical metabolism, body temperature, sexual function, hormones, and waking and sleeping. It is believed that, together with the limbic system, it plays an important part in the expression of mood, affect, and emotion.
Limbic system:	Often called the "visceral brain," this evolutionary old part of the subcortex includes the hippocampus, cingulate gyrus, amygdala, and septum. It is generally associated with the regulation of emotions and emotion-producing stimuli such as hunger and sex. It seems to coordinate sensory data with bodily needs and is also involved in memory.

Midbrain reticular formation:	This part of the larger brain area of the reticular formation lying in the brainstem is involved in homeostatic control of the body. It sends messages to the hypothalamus, preoptic area, and septum, and both sends and receives them from the limbic system. The reticular formation provides a mechanism for sending specific impulses throughout the central nervous system and for evoking generalized responses such as waking, sleeping, and alerting. The Central Gray is part of the midbrain reticular formation.
Preoptic area:	This part of the subcortex is found just behind the point where visual signals cross to the brain (optic chiasm). Although not part of the hypothalamus proper, it is related intimately, both anatomically and physiologically.
Septum:	A functionally intermediate structure between the hippocampus, the preoptic area, and the hypothalamus. It is a correlative center, relaying visceral information to the hippocampus and amygdala, among other areas. It may be connected with the sense of smell.
Stria terminalis:	A winding bundle of fibers, like a cable, which leads impulses from the amygdala and is connected to the preoptic area and hypothalamus.
Thalamus:	A mass of gray matter located at the floor of the brain near the third ventricle (brain hole). It correlates sensory information regarding the external environment and controls the facial muscles under stress. It can be viewed as a center for sorting and analyzing sensation.
Trigeminal nerve:	One of the cranial nerves which goes directly from the brain to the face. It controls facial muscles and receives signals from them.

Supplementary Readings

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